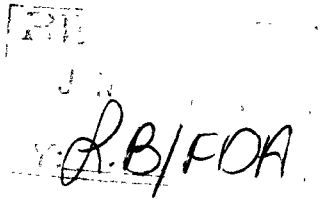
December 25, 2003

Office of Nutritional Products
Labeling and Dietary Supplements (HFS-820)
Center for Food Safety and Applied Nutrition
Food and Drug Administration
5100 Paint Branch Pkwy.,
College Park, MD 20740




We are writing to provide the FDA with a premarket notification.

**Name of the new dietary ingredient**: Sea Buckthorn extract, derived from the leaves of the Sea Buckthorn plant.

**Latin name**: (Hippophae rhamnoides L)

**General Description:** A shrub or small tree, native from Europe to the Altai mountains in western and northern China and the Himalayan mountains. Sea Buckthorn was introduced into North America in 1923. As a food, its astringent fruits are highly acidic and with a high vitamin C content, used as a juice in Asia, Europe and the United States. Its pulp and seed oil are used as a topical skin ointment and as a dietary supplement because of its high vitamin content. There has been a growing interest in many countries to commercialize Sea Buckthorn (*Hippophae rhamnoides* L, Elaeagnaceae) and its products. Although not a legume, roots of Sea Buckthorn (known as oblepiha in Russia) are host to the nitrogen-fixing symbiotic rhizobium. Roots, bark, and leaves contain essential oil, essential fatty acids, flavonoids, serotonin, polyphenols, minerals, amino acids, and other substances of interest to human health. Some essential fatty acids have strong antioxidant activity, which have received increasing attention for their ability to inhibit cancer and atherosclerosis, the enhancement of immune function, and reduction of fat accumulation. In Russia, a long time study [attached within this document] has been underway to develop cultivars of Sea Buckthorn adapted to extreme ecological conditions under different climatic zones of the former Soviet Republics and Eastern European countries.

**Ingredients of each dietary supplement capsule:** Each 0.6 gram tablet contains:

**Active ingredient:** 0.02 gram of a dry purified extract of the polyphenol complex of gallo-ellagi-tannins produced from Hippophae rhamnoides (Sea Buckthorn).

**Inactive ingredients:** Sugar, Cocoa, Vanilla, Stearic Acid.

**Suggested use:** As a dietary supplement, one to two tablets daily, when needed.

*Following is an article written by the Russian manufacturer of the dietary supplement we intend to distribute in the United States:*

# PROSPECTS OF GREEN GRASSY SHOOTS OF SEABUCKTHORN (HIPPOPHAE RHAMNOIDES L.) AS A SOURCE FOR COMMERCIAL PRODUCTION OF HIPORAMIN

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Seabuckthorn (Hippophae rhamnoides L.), and extracts from it, attracted last year's great attention of the scientists of many countries as the source for production of various biologically active substances, pharmaceutical forms, vitamins, dietary supplements and food additives. The basic organs for their preparation are fruits, seeds and leaves of the plants (fatty oil, juice etc.). Biologically active principals of Sea Buckthorn are vitamins, carotenoids, lipids, containing essential polyunsaturated fatty acids (PUFA), flavonoids, tannins, etc. In All-Russian Research Institute of Medicinal and Aromatic Plants there was found as a result of perennial systematic research work, that the leaf extracts possess a high antiviral activity, while the active principals of polyphenol fraction were hydrolysable gallo- and ellagi-tannins (strictinin, isostrictinin, casuarinin, casuarictin, pedunkulagin etc.).

Due to considerable difficulties of manual purchase of Sea Buckthorn leaves in the commercial scale for extract production there has been worked out a mutual project of two institutes on the optimal conditions of the purchase of green herbaceous shoots of Sea Buckthorn and to find out their suitability for Tannin production. Therefore a comparative study of tannin contents in green herbaceous shoots and leaves, dependently on the size of cuttings of the shoots, kept in different vegetation periods, age of plants, as well as sex of plants and eco-geographic factors, are of significant interest. Forming cuts were carried out with two populations of Sea Buckthorn Chuiskaya and Podarok sadu .

As a result there has been found a definite dependence of the mass of the green vegetative source accumulation and the length of the shoots, producing the maximal yield of the vegetative mass, dynamics of the tannin fraction accumulation as well as the total tannin content in the polyphenol fraction. There were found that the tannin fraction yields were from 34.3 to 39.4 % dependently the period of the plant vegetation. The yields fluctuations at 8-age and 5-age-old plants were less noticeable and were 29.29-23,84 %. Otherwise the tannin fraction yields were dependent on the shoots length. Short cuts (up to 7 cm) yield 27.1-31.1 % of tannin fraction, medium cuts (up to 14 cm) give 25.04-30.65 % of the key fraction, while long cuts (up to 21 cm) 23.62-28.35 %. The yield of the tannin fraction was also dependent on the period of shoots purchase, the latter being dependent on the on the ratio of leaves and stems in the vegetation mass, containing cuts of a definite size and age of shoots with the predominant accumulation of tannins in leaves.

On purchase of short cuts the maximal yield of the extract was noted at the end of the phase of intense growth (the first decade of August) or in the middle of intense growth period. There was mentioned a reverse correlation of the extract yield with the length of the shoots.

Tendency of the seasonal dynamics of tannin accumulation in extract and in dry leaves were approximately the same. The highest content of the tannin fraction in the plant (on dry weight) was found in the first part of July in all variants, while dependently on shoots length it was within 18.0-20.9 %, the maximum was found in the first part of July. But at the end of intense growth phase there was found its diminishing.

Dynamics of tannin accumulation in the vegetation period was in a considerable degree dependent on the length of the shoot cuts. In short shoots (7 cm) there were found a smooth increase of the tannin contents up to the middle of July, while in August there was found some tendency to its diminishing. In shoots (up to 14 cm) there were shown uneven change of tannin accumulation, the maximum being reached in the first decade of July. The analysis of 21 cm shoots has confirmed the more high total tannin content up to middle July, while up to August some diminish was mentioned. Thus the maximal accumulation of the total tannins occurs at the phase of intense growth, following its diminishing. There was not found a strict difference in tannin content in the plant source and in the tannin fraction dependently the age of plants (2-8 years). From the experimental data one can see the yield of the extract from leaves and the shoots in different populations of Sea Buckthorn, while there were not found marked differences in results produced for different populations and the samples of different ages.

*Scientific studies on the efficacy of potential benefits as a dietary supplement include this study:*

**Cytoprotective and Immunomodulatory Potential Of Seabuckthorn**

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**Abstract**

The anti-oxidant and immunomodulatory properties of Sea Buckthorn were studied *in vitro* using rat spleenocytes and macrophages and *in vivo* using male albino rats. Addition of chromium or sodium nitroprusside (SNP) to the cells resulted in enhanced cytotoxicity, free radical generation; and decreased glutathione (reduced) levels and glutathione peroxidase activity. Chromium also caused a significant inhibition of both lipopolysaccharide and concanavalin A stimulated lympholcytes proliferation. The alcoholic leaf and fruit extracts of

Seabuckthorn at a dose of 500 □ g/ml and 1mg/ml respectively inhibited chromium and SNP induced cytotoxicity significantly as determined by acridine orange/ethidium bromide staining and lactate deydrogenase leakage in both lymphocytes and macrophages. These extracts also inhibited chromium and SNP induced free radical production, apoptosis and restored the antioxidant status to that of control cells. The leaf extract itself stimulated lymphocyte proliferation even in the absence of stimulants like concanavalin A and lipopolysaccharide. The extract alone stimulated IL-2 and □ -IFN production in the absence of Con A and also inhibited chromium induced decline in IL-2 and □ -IFN production, but did not alter IL-4 production. Administration of chromium to male albino rats significantly decreased reduced glutathione (GSH), and increased malondialdehyde, (MDA) and creatine phosphokinase (CPK) levels and enhanced glutamate oxaloacetate transferase (GOT) and glutamate pyruvate transferase (GPT) levels in the serum. Different doses of alcoholic leaf extract of seabuckthorn were evaluated for protection against chromium induced oxidative stress. The results show that the leaf extract at a concentration of 100 and 250 mg/kg bodyweight protected the animals from chromium induced oxidative injury significantly. Administration of leaf extract along with chromium significantly inhibited chromium-induced immunosuppression. The extract did not affect the humoral response but protected the animals from chromium-induced inhibition of DTH response. These observations suggest that the leaf extract of seabuckthorn has significant, cytoprotective and immunomodulatory properties and specifically activates the cell-mediated immune response.

*And another study, pointing to tannins contained in foods and beverages...*

**Tannins, Xenobiotic Metabolism and Cancer Chemoprevention in Experimental Animals.**

**Nepka C, Asprodini E, Kouretas D.**

**Cytopathology Laboratory, Serres, Greece.**

Tannins are plant polyphenolic compounds that are contained in large quantities in food and beverages (tea, red wine, nuts, etc.) consumed by humans daily. It has been shown that various tannins exert broad cancer chemoprotective activity in a number of animal models. This review summarizes the recent literature regarding both the mechanisms involved, and the specific organ cancer models used in laboratory animals. An increasing body of evidence demonstrates that tannins act as both anti-initiating and antipromoting agents. In view of the fact that tannins may be of valid medicinal efficacy in human clinical trials, the present review attempts to integrate results from animal studies, and considers their possible application in humans. Carcinogenesis 1996 Apr;17(4):821-8

*The following study does not attempt to show a relationship between Sea Buckthorn and our product and the study's conclusion; rather it is offered to support the use of Sea*

*Buckthorn as a dietary supplement and its safety when administered to human subjects as suggested:*

- **Effect of Sea Buckthorn on Liver Fibrosis: A Clinical Study**

  **Gao ZL, Gu XH, Cheng FT, Jiang FH.**

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  AIM: To appraise the effect of Sea Buckthorn (Hippophae rhamnoides) on cirrhotic patients. METHODS: Fifty cirrhotic patients of Child-Pugh grade A and B were randomly divided into two groups: Group A as the treated group (n=30), taking orally the Sea Buckthorn extract, 15 g 3 times a day for 6 months. Group B as the control group (n=18), taking vitamin B complex one tablet, 3 times a day for 6 months. The following tests were performed before and after the treatment in both groups to determine LN, HA, collagens types III and IV, cytokines IL-6 and TNFalpha, liver serum albumin, total bile acid, ALT, AST and prothrombin time. RESULTS: The serum levels of TNFalpha, IL-6, laminin and type IV collagen in group A were significantly higher than those in the control group. After a course of Sea Buckthorn treatment, the serum levels of LN, HA, collagen types III and IV, total bile acid (TBA) decreased significantly as compared with those before and after treatment in the control group. The Sea Buckthorn notably shortened the duration for normalization of aminotransferases. CONCLUSION: Sea buckthorn may be a hopeful drug for prevention and treatment of liver fibrosis.

  PMID: 12854177 [PubMed - indexed for MEDLINE]

*Again another study, shown here not to imply that our product creates a medicinal end result; rather that it is safe for human consumption:*

**Effects of Total Flavones of Hippophae Rhamnoids L (Sea Buckthorn) on Cardiac Function and Hemodynamicsin Healthy Human Subjects**

**Wang B, Feng Y, Yu Y, Zhang H, Zhu R**
***Translated and edited by Rich Nature Lab.***

**Abstract**
This study was a randomized, double blind, placebo-controlled evaluation of the effects of total flavones of Hippophae Rhamnoids L (TFH) in healthy subjects. Healthy volunteers were divided into the TFH group (22 cases) and the placebo group (20 cases). Changes in cardiac function and hemodynamics were measured by the Admittance method and the STI Method. After oral administration of 10mg of TFH, it was shown that the ratio of pre-ejection

period (PEP) to left ventricular ejection time (LVET), the ratio of isovolumic contraction time (ICT) to LVET, and ICT in the TFH group were significantly decreased ($P<0.05$). Stroke volume (SV) in this group was significantly increased ($P<0.05$). There were also increases in cardiac output (CO), cardiac index (CI), length index (LI), stroke work index (SWI), and cardiac work index (CWI) in this group. Total peripheral resistance (TPR) was greatly decreased ($P<0.05$) and compliance (C) was increased ($P < 0.05$). No differences were observed in any of these indexes in the placebo group ($P>0.05$). These results suggest that TFH may not only improve myocardial contractility and strengthen cardiac pump function, but also may decrease peripheral vessel resistance and increase vessel elasticity.

**Background**

Total flavones of Hippophae Rhamnoids L (TFH) are extracted from the fruit or leaf of Hippophae, which is also known as Sea Buckthorn. It was previously reported that TFH could be used to treat angina pectoris, arrhythmia and hyperlipaemia 1, 2 . Since TFH had improved cardiac function in previous anesthetized mouse studies, this study was designed to investigate the effects of TFH on cardiac function and hemodynamics in healthy human subjects. The prognosis for patients with cardiac failure is poor due to insufficient treatment options. ***TFH is not only plentiful but also nontoxic.*** Since this and previous studies suggest that TFH can improve cardiac function, further research is warranted.

We believe that the use of Sea Buckthorn as a dietary supplement as recommended, and based on the long history of use and other evidence of safety, establishes that the dietary ingredient, when used under the conditions recommended or suggested in the labeling of the dietary supplement, will be reasonably be expected to be safe.

Sincerely,

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